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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,882	03/22/2004	Christopher J. Frederickson	D6489	9873

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EXAMINER	
HUYNH, CARLIC K	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
04/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,882	FREDERICKSON, CHRISTOPHER J.	
	Examiner	Art Unit	
	CARLIC K. HUYNH	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *7-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of applicant's amendments and remarks filed on January 28, 2008 is acknowledged.

Status of the Claims

1. Claims 1-34 are pending in the application, with claims 7-34 having been withdrawn from consideration, in response to the restriction requirement filed on May 31, 2007. Accordingly, claims 1-6 are being examined on the merits herein.

The rejections under 35 U.S.C. 112, first paragraph to claims 1 and 5-6 for not being enabled for preventing a zinc-mediated brain injury have been withdrawn in view of Applicant's amendments.

The obviousness-type double patenting rejection to claims 1 and 5-6 as being unpatentable over claims 25, 39, 41, 51, 56, and 60 of copending Application Frederickson et al. (10/929,924) has been withdrawn because claims 24-78 have been withdrawn from consideration.

Drawings

2. The drawings are objected to because the copies are too dark. Specifically, Figures 2A, 4A-F, 6, and 10A-D are too dark and thus prevent their proper interpretation. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid

abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Response to Arguments

3. Applicant's amendments, see "Remarks" filed on January 28, 2008, with respect to "drawing objection" have been fully considered and are not persuasive. Applicant adjusted the drawings to increase the light and tissue detail. However, Examiner points out that figures 2A, 4A-F, 6, and 10A-D are still too dark and the tissue detail is still poor.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Montécot et al. (Neuroscience, 1998, Vol. 84, No. 3, pp. 791-800).

Montécot et al. teach that system administration of 7-nitroindazole, a selective inhibitor of neuronal nitric oxide synthase (nNOS), inhibited hippocampal NOS activity and protects neurons from seizure-induced toxicity (abstract).

It is noted that the instant claims entail only the step of administering an agent, e.g. 7-nitroindazole, to inhibit nitric oxide synthase in neurons.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 102(b).

Response to Arguments

5. Applicant's arguments, see "Remarks" filed on January 28, 2008, with respect to "Rejections under 35 U.S.C. § 102" have been fully considered and are not persuasive.

Applicant argues that "the basis for this rejection is that the instant claims entail only the step of administering an agent, e.g., 7-nitroindazole, to inhibit nitric oxide synthase in neurons. See page 7 of the Office Action." Applicant further argues that "the Montécot et al. reference does not teach or describes a method of inhibiting zinc release from neurons by inhibiting nitric oxide synthesis in neurons. More significantly, it appears the Montécot et al. reference does not recognize or even mention release of zinc by neurons. In contrast, the Montécot et al. reference

appears to be using a nitric oxide synthase inhibitor as a means for controlling cerebral blood flow". Applicant also argues that "claims are anticipated if, and only if, **each and** every element as set forth in the claim is found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 2 USPQ2d 1051 (Fed. Cir. 1989)".

In response, Examiner points out that the instant claims are directed to a method of inhibiting zinc release from neurons comprising administering at least one agent that inhibits nitric oxide synthesis and as such, the teaching in Montécot et al. of using a nitric oxide synthase inhibitor as a means for **controlling cerebral blood flow** is not given any consideration. The Examiner also points out that the amended claim 1 still contains the single step of administering an agent, e.g., 7-nitroindazole, to inhibit nitric oxide synthase in neurons. The Examiner further points out that the inhibition of zinc release is an inherent property of nitric oxide synthase inhibition and thus each and every element of the instant claims are taught in Montécot et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frederickson (International Review of Neurobiology, 1989, Vol. 31, pp. 145-238) in view of Bagetta et al. (Biochemical and Biophysical Research Communications, 2002, Vol. 291, pp. 255-260) and Suh et al. (Brain Research, 2001, Vol. 895, pp. 25-32).

Frederickson defines zinc-containing neurons as neurons that selectively concentrate zinc in their axonal boutons (pp. 196-197). Thus, the zinc is stored in the presynaptic vesicles of the zinc-containing neurons. Frederickson teaches that the mossy fiber axons of the hippocampus are the most thoroughly studied of the zinc-containing fiber systems (p. 197). Frederickson further teaches that zinc plays a role in epilepsy (p. 216). CNS zinc levels are abnormal in the brains of seizure prone laboratory animals and in the brains and body fluids of human patients with seizure related disorders (pp. 216-217). Furthermore, the heaviest concentrations of zinc-containing boutons are in the seizure-prone limbic regions of the brain, e.g. the hippocampus (pp. 216-217).

Frederickson does not teach the involvement of nitric oxide synthase, either nNOS or eNOS, in seizures and chelating zinc to treat seizures.

Bagetta et al. teach enhancement of the expression of neuronal nitric oxide synthase (nNOS) by administration of tacrine triggers limbic seizures and damage to the hippocampus in rats and that pretreatment with 7-nitroindazole, a selective inhibitor of nNOS, prevented the seizures and abolished neuronal cell death in the hippocampus (abstract).

Suh et al. teach that chelatable zinc ions released from zinc-enriched synaptic vesicles are involved in seizure-induced neuronal death in the hippocampus (abstract).

Accordingly, absence the showing of unexpected results, it would have been obvious to a person of skill in the art at the time of the invention to employ the teachings of Frederickson to treat epilepsy or seizures because the compounds of Bagetta et al. are the inhibitor of nNOS, 7-nitroindazole and according to Bagetta et al., 7-nitroindazole treats epilepsy and seizures.

The motivation to combine the teachings of Frederickson to the compounds of Bagetta et al. is that the compounds of Bagetta et al. are the inhibitor of nNOS, 7-nitroindazole and that such compounds, 7-nitroindazole, treat epilepsy and seizures.

Accordingly, absence the showing of unexpected results, it would have been obvious to a person of skill in the art at the time of the invention to employ the teachings of Frederickson to treat epilepsy or seizures because the compounds of Suh et al. are chelatable zinc and according to Suh et al., chelated zinc treats epilepsy and seizures.

The motivation to combine the teachings of Frederickson to the compounds of Suh et al. is that the compounds of Suh et al. are chelatable zinc and that chelating zinc treats epilepsy and seizures.

It is noted that "It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose" and "It is obvious to combine two compositions taught by the prior art to be useful for the same purpose to form a third composition that is to be used for the very same purpose". *In re Kerkhoven*, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Response to Arguments

7. Applicant's arguments, see "Remarks" filed on January 28, 2008, with respect to "Rejections under 35 U.S.C. § 103" have been fully considered and are not persuasive.

Applicant argues teaches that "zinc has no clear role in seizure pathophysiology." Applicant points where Frederickson states:

> The foregoing encourages the general notion of a zinc role in seizure pathophyiology, but closer view of the evidence does not lead to any simple, unitary hypothesis about the underlying mechanisms. For example, whereas mice genetically prone to seizures have elevated brain zinc .... genetically seizure-prone rats have 47% less zinc in the hippocampal mossy fiber region than control rats .... Similarly, zinc in the serum of seizure-prone baboons...is apparently elevated .... whereas the CSF of children undergoing "fifth-day fits"..., and the serum of preeclamptic women.., are characterized by subnormal zinc concentration. In adult patients suffering from epileptic disorders, some investigators have found changes in serum zinc ....but other evidence indicates that neither epilepsy nor anticonvulsant drug therapy is consistently associated with any abnormalities of serum zinc .... These findings suggest that the amount of zinc in the brain, CSF, and serum may vary depending on the eitology [sic], clinical history, and status of seizure-prone individuals or populations. Oral zinc supplements have been used as a therapy for Wilson's disease to lower the copper levels in those patients. Despite two-fold increases in serum zinc, no seizure disorders have been reported ....
> (Page 217 of the Frederickson reference).

Accordingly, the Frederickson suggests that zinc levels in brain vary depending on individual or population investigated.

Applicant further argues "the Bagetta et al. reference teaches tacrine-induced seizures induce nNOS expression and pretreatment with an nNOS inhibitor prevents seizures and neuronal cell death; and the Suh et al. reference discusses that chelatable zinc release is involved in seizure-induced neuronal death" and that " none of the cited references either alone or in combination teach, suggest or even remotely discuss methods for inhibiting zinc release in neurons by reducing nitric oxide level in the neurons".

In response, Examiner points out Frederickson teaches zinc may have a role in seizure pathophysiology. Frederickson teaches that zinc plays a role in epilepsy (p. 216). CNS zinc

levels are abnormal in the brains of seizure prone laboratory animals and in the brains and body fluids of human patients with seizure related disorders (pp. 216-217).

Examiner further points out that Bagetta et al. provide a link between seizure and nNOS expression. In fact Bagetta et al. teach enhancement of the expression of neuronal nitric oxide synthase (nNOS) by administration of tacrine triggers limbic seizures and damage to the hippocampus in rats and that pretreatment with 7-nitroindazole, a selective inhibitor of nNOS, prevented the seizures and abolished neuronal cell death in the hippocampus (abstract).

Examiner also points out that Suh et al. provide a link between zinc and seizure. In fact, Suh et al. teach that chelatable zinc ions released from zinc-enriched synaptic vesicles are involved in seizure-induced neuronal death in the hippocampus (abstract). The teachings of Suh et al. support the findings in Frederickson, where zinc may have a role in seizure pathophysiology.

Taken together, the teachings of Frederickson, Bagetta et al. and Suh et al. teach the limitations of the instant claims for reasons stated above and of record.

Conclusion

8. No claims are allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

ckh